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Microcontainers improve oral bioavailability of furosemide

Line Hagner Nielsen[1], Ana Melero[2], Stephan Sylvest Keller[1], Thomas Rades[3], Anette Müllertz[3], Anja Boisen[1]

[1]Department of Micro- and Nanotechnology, Technical University of Denmark, Kgs. Lyngby, Denmark
[2]Department of Pharmacy and Pharmaceutical Technology, University of Valencia, Valencia, Spain
[3]Department of Pharmacy, University of Copenhagen, Copenhagen, Denmark

lihan@nanotech.dtu.dk

INTRODUCTION & AIM

Microcontainers have been proposed as a novel approach to improve the oral bioavailability of drugs[1]. Microcontainers are small polymeric cylinders on a flat base (Fig. 1). The microcontainers allow for protecting the drug in the harsh environment of the stomach and also provide the possibility of unidirectional release of the drug directly to the small intestinal epithelium (Fig. 2).

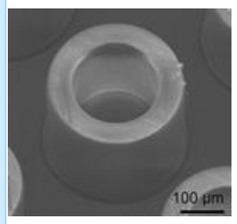


Fig. 1: Image of a polymeric microcontainer

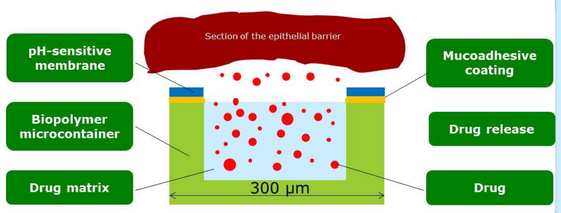


Fig. 2: Illustration showing the microcontainer concept including the unidirectional release

AIM: To investigate the *in situ* interaction between the microcontainers and the small intestinal membrane and to evaluate the *in vivo* performance of the microcontainers filled with amorphous sodium salt of furosemide (ASSF) after oral dosing to rats (Fig. 3).

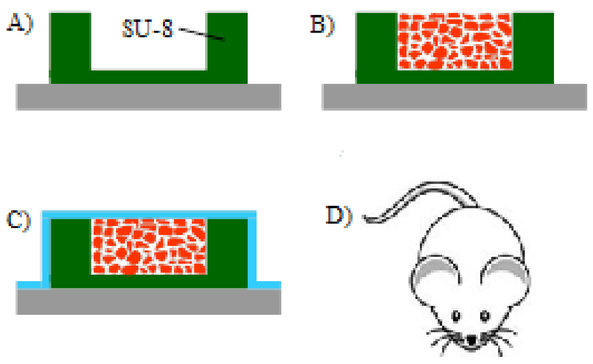


Fig. 3: Illustrations of the experimental methods. A) Fabrication of SU-8 microcontainers. B) Filling with drug powder (amorphous furosemide sodium salt). C) Spray coating of a lid of Eudragit® L100 or chitosan. D) *In situ* intestinal perfusion studies and oral bioavailability studies in rats of the drug-filled microcontainers coated with Eudragit® L100

METHODOLOGY

Fabrication of microcontainers

SU-8 (epoxy-based photoresist) microcontainers were fabricated through two steps of photolithography to define the base and the walls (Fig. 4). This resulted in microcontainers with inner diameter of 223 µm (Fig. 1). Silicon wafers supporting the microcontainers were cut into squares of 12.8 x 12.8 mm^2 resulting in 25 x 25 microcontainers with a pitch of 450 µm (Fig. 5)[2].

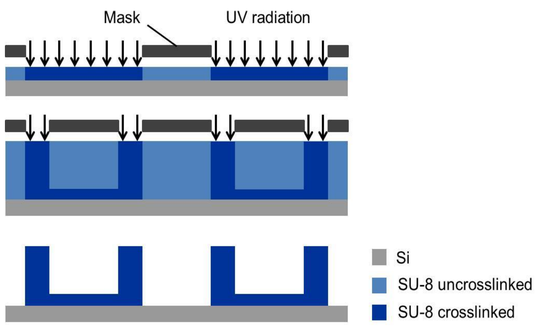


Fig. 4:Scematic of the fabrication process of SU-8 microcontainers

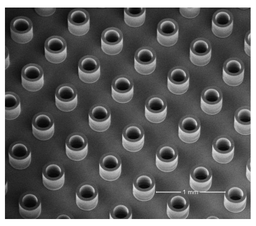
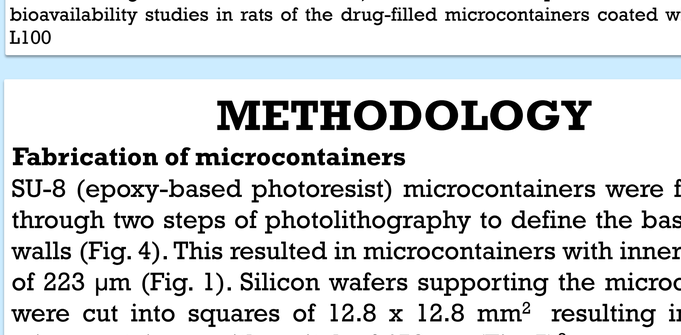


Fig. 5: SU-8 microcontainers on a silicon wafer

Preparation of the amorphous sodium salt of furosemide[3]



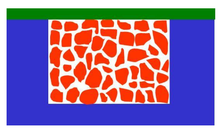
Filling of microcontainers with ASSF

Powder drug distribution — Removal with air gun

The microcontainers were filled with ASSF by first distributing the powder onto the squares with microcontainers and subsequently, removing the powder in between the microcontainers with an air gun[4].

Coating of drug-filled microcontainers

The drug-filled microcontainers were spray coated with a lid of either the pH-sensitive polymer, Eudragit® L100 or the mucoadhesive polymer, chitosan.



Eudragit® L100 coated microcontainer

Chitosan coated microcontainer

In situ intestinal perfusion studies

In situ intestinal perfusion studies were performed in fasted rats with a weight of approximately 200 g (Fig. 6)[5].

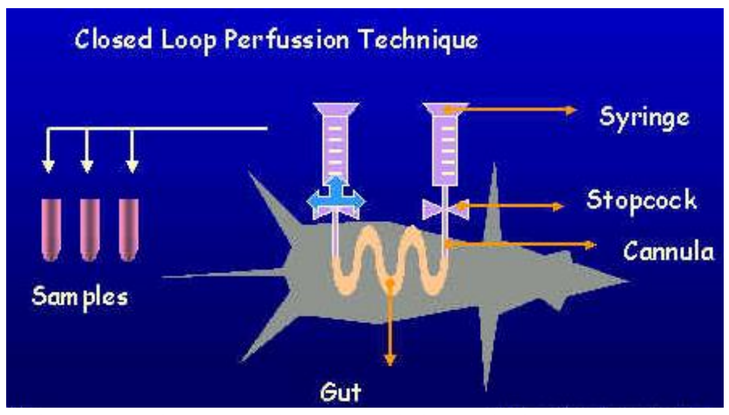
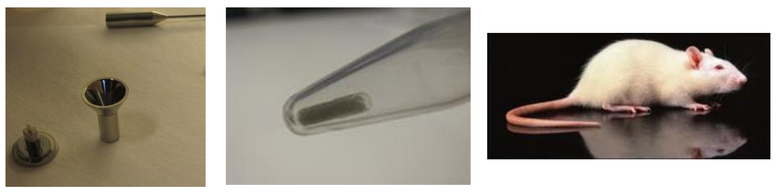


Fig. 6: The set-up for the *in situ* intestinal perfusion studies in rats

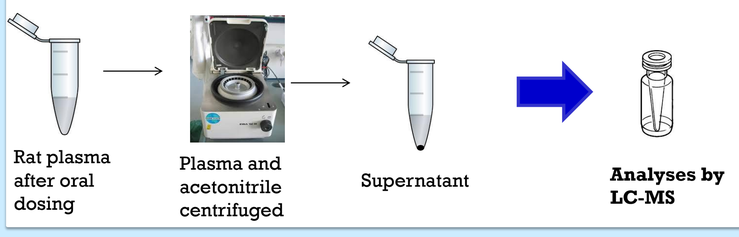
The coated, ASSF-filled microcontainers were dosed with 10 mL of phosphate buffer at pH 6.5 directly to the small intestine. As controls, a solution of furosemide in phosphate buffer, as well as empty microcontainers, were dosed. Blood samples (200 µL) were drawn every 5 min for 30 min. After the 30 min, the small intestine was harvested from the rat and imaged under a UV and fluorescence microscope.

Oral bioavailability study in rats



The ASSF-filled microcontainers were coated with Eudragit® L100 and filled into capsules (size 9). As control ASSF was filled into capsules and subsequently, coated with Eudragit® L100 were used. The capsules were dosed orally to rats (~300 g) and 10 blood samples were taken during 24h.

Analysis of ASSF in the plasma samples:



Rat plasma after oral dosing → Plasma and acetonitrile centrifuged → Supernatant → **Analyses by LC-MS**

RESULTS

Preparation of the ASSF

ASSF was successfully prepared by spray drying. The drug form showed promising *in vitro* properties in terms of high solubility and increased dissolution rate at pH 6.5[4].

Filling of microcontainers with drug powder

Loading of drug powder into the microcontainers was shown to be a very useful method for quickly filling the microcontainers while avoiding deposition of drug powder in between the microcontainers (Fig. 7). Moreover, the method can be utilised for all type of drugs.

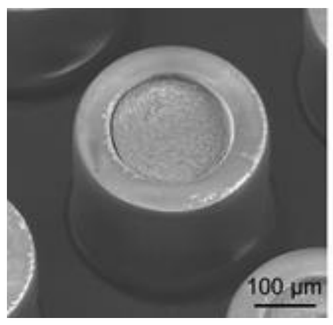


Fig. 7: A microcontainer after drug filling

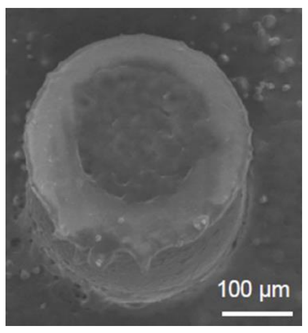


Fig. 8: A microcontainer after drug filling and spray coating with a polymer layer

Coating of drug-filled microcontainers

Fig. 8 shows a drug-filled SU-8 microcontainer coated with either Eudragit® L100 or chitosan. The thickness of the polymer layer was in both cases measured to be approximately 10 µm.

In situ intestinal perfusion studies

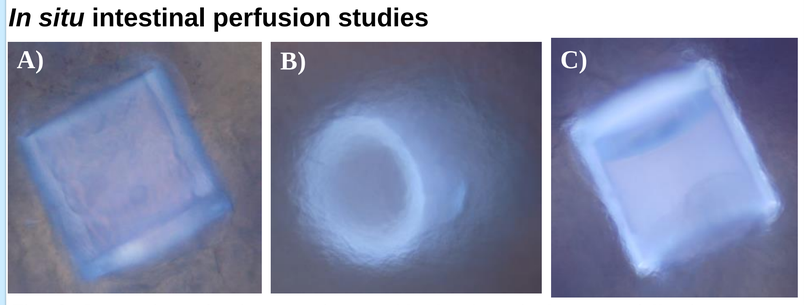


Fig. 9: Interaction of microcontainers with the intestinal mucus following *in situ* intestinal perfusion studies. Microcontainers were filled with ASSF and coated with a lid of A) Eudragit® L100 and B) chitosan. C) empty microcontainers without drug and coating

The microscope images of the small intestine after the perfusion studies showed that the microcontainers interacted with the mucus in the small intestine, and the microcontainers were engulfed by the intestinal mucus (Fig. 9). By these qualitative results, it was observed that also without coating, the microcontainers interacted with the intestinal mucus (Fig. 9C).

Oral bioavailability study in rats

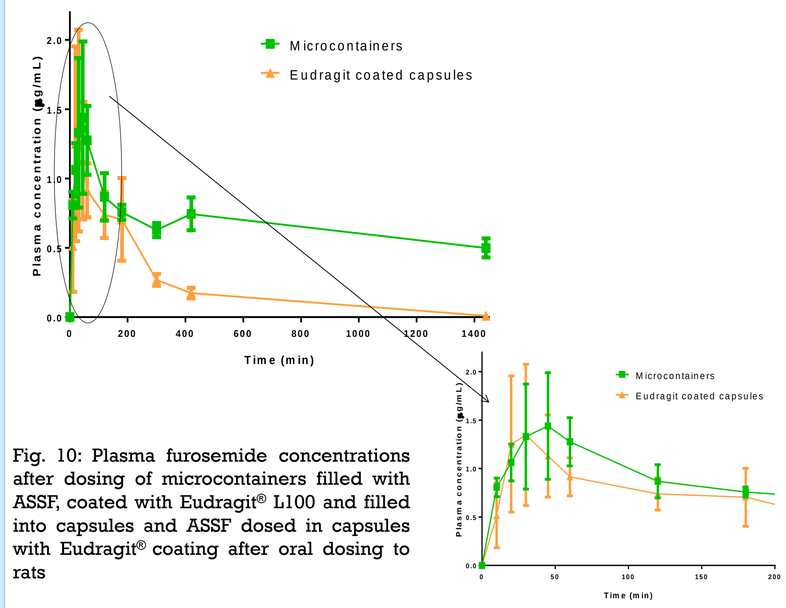


Fig. 10: Plasma furosemide concentrations after dosing of microcontainers filled with ASSF, coated with Eudragit® L100 and filled into capsules and ASSF dosed in capsules with Eudragit® coating after oral dosing to rats

After the oral dosing of the rats with either ASSF-filled microcontainers or ASSF filled into capsules, the plasma concentrations were initially similar, but the microcontainers exhibited a prolonged release of ASSF (Fig. 10) resulting in a bioavailability of 220% compared to the drug-filled capsules (Table 1).

Table 1: Noncompartmental pharmacokinetic parameters of ASSF following oral administration to rats

	Eudragit coated microcontainers (Mean±SEM)	Eudragit coated capsules (Mean±SEM)
T_{max} (min)	34.2±9.7	48.0±7.3
C_{max} (µg/mL)	1.9±0.48	1.7±0.68
$AUC_{0\text{-}180\ min}$	179.6±33.3	152.2±39.2
$AUC_{0\text{-}1440\ min}$	1696.4±299.7	326.1±55.0
Relative bioavailability (%)	220.2±43.2	-

CONCLUSION

- SU-8 microcontainers with inner diameter of 223 µm were fabricated
- Microcontainers were filled with powder drug using a fast and widely-applicable method.
- The microcontainers interacted with the intestinal mucus layer
- In rats ASSF in microcontainers exhibited a oral bioavailability of 220% compared to capsules filled with ASSF

- **Microcontainers are proposed as a promising oral drug delivery system**

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